



# Status epilepticus (SE) and midazolam

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UIHC, May 2009

# Objectives

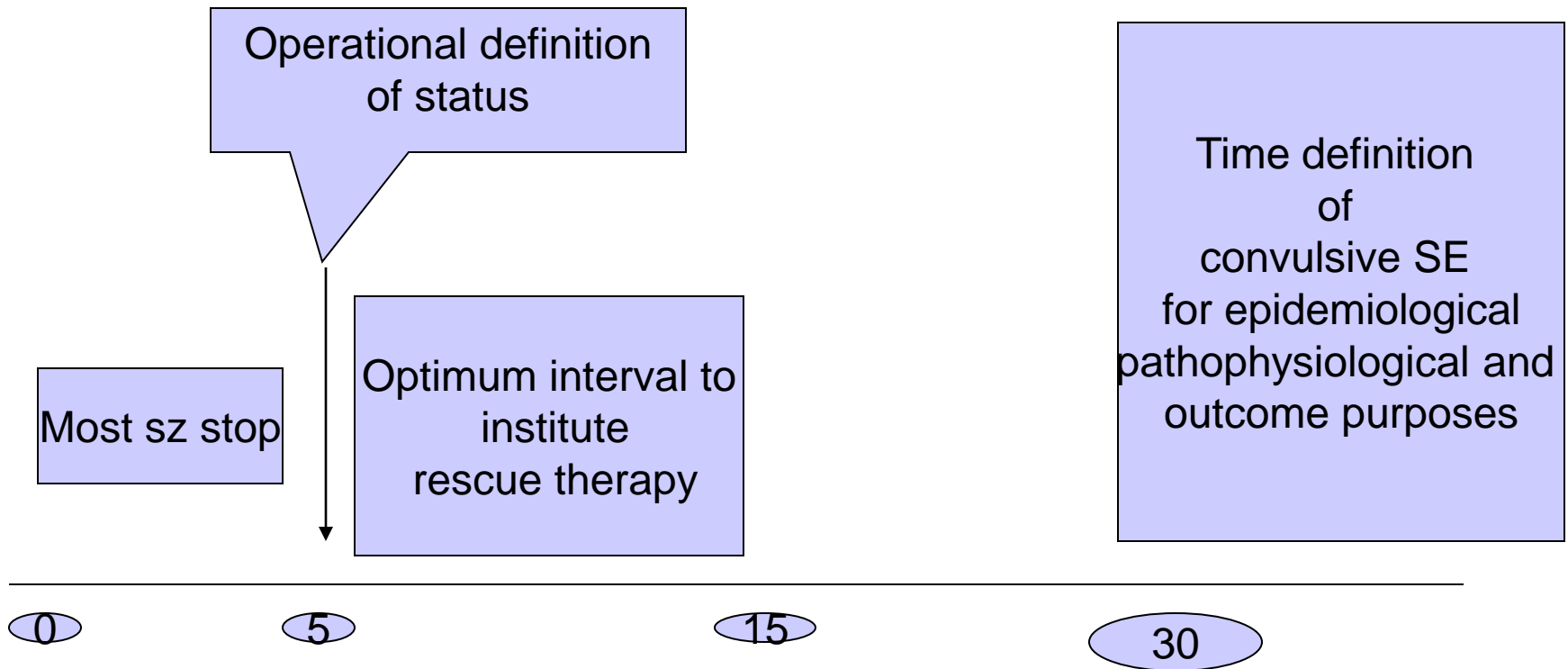
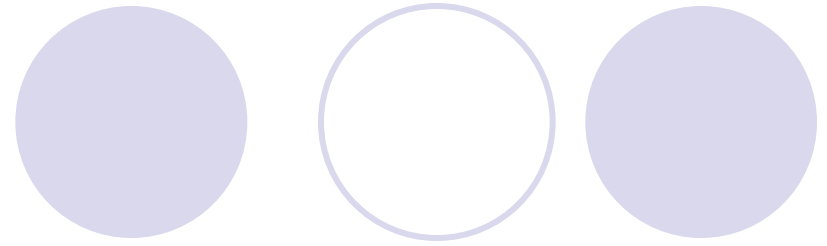
- To define SE
- Learn about the etiology of SE
- Morbidity/ Mortality of SE
- Prevention and treatment

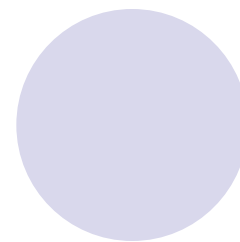
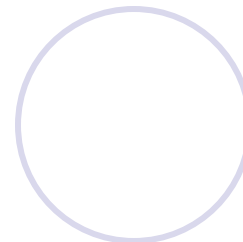
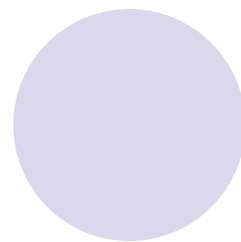
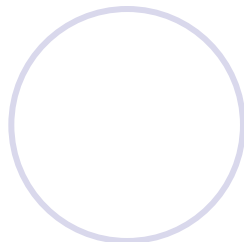
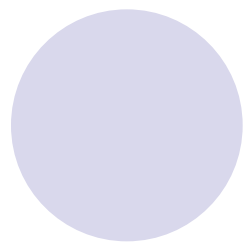
# SE- Definition

- “A seizure that shows **no clinical signs of arresting** after a duration encompassing the great majority of seizures of that type in most patients OR recurrent seizures without interictal resumption of baseline central nervous system function”
- Conventional temporal definition- 30 minutes
- Incidence- 20/100000/year

# SE definition

- Timeline in minutes





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# Who Is at Risk for Prolonged Seizures?

Shlomo Shinnar, MD, PhD

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This article reviews how long seizures last and how frequently seizures are prolonged, risk factors for prolonged seizures, and a conceptual framework that links them. These data are derived from studies of patients with a first unprovoked seizure, studies of children with febrile seizures, studies of population-based and community-based cohorts with newly diagnosed epilepsy and patients with refractory epilepsy, and treatment trials. Prolonged seizures that exceed 5 to 10 minutes are relatively common, and the key factor in the identification of those at risk

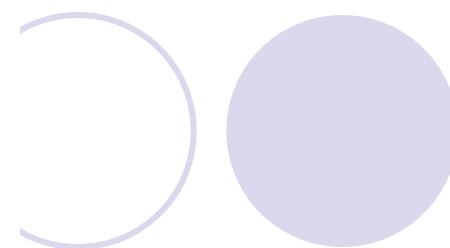
is a history of a prior prolonged seizure. A subgroup of patients with seizures is predisposed to prolonged although not necessarily frequent seizures, which are associated with increased morbidity, increased emergency department visits, and a decreased quality of life. This article also addresses criteria used to justify treatment of a seizure once it has continued longer than 5 minutes and the rationale for such treatment.

**Keywords:** seizure risk; prolonged seizures; status epilepticus

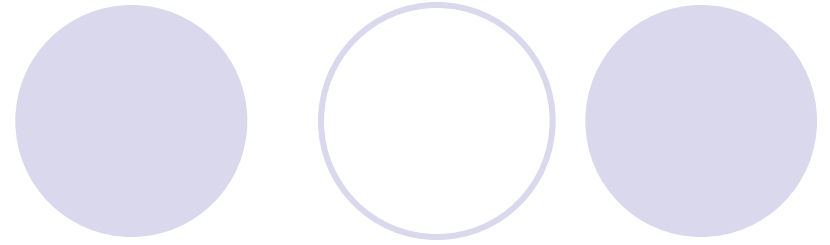
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In a prospective study of 407 children with a first unprovoked seizure, Shinnar et al<sup>6,9-11</sup> reported that seizures lasting more than 5 minutes were common and occurred

in approximately half the children. Seizure durations were estimated by using a structured interview and reviewing the medical records. For prolonged seizures, ambulance call sheets and emergency department records were also used.<sup>10</sup> In this study, the first seizure lasted 5 minutes or more in 50% of cases, 10 minutes or more in 29%, 20 minutes or more in 16%, and 30 minutes or more in 12% of cases. Seizures with partial onset were more likely to be prolonged (62%  $\geq$  5 minutes and 20%  $\geq$  30 minutes) than seizures of generalized onset (42%  $\geq$  5 minutes and 6%  $\geq$  30 minutes;  $P < .001$ ). Etiology and age of onset did not affect seizure duration, although, as expected in a new-onset community-based cohort, relatively few children presented with remote symptomatic etiology.



# Classification of SE



## Semiologic versus etiologic classification

- Convulsive
- Non convulsive
- Neonatal

# Classification of SE

## Etiologic

**TABLE 1.** *International League Against Epilepsy's recommended classification of status epilepticus according to etiologies (Gastaut, 1983; ILAE Commission on Epidemiology and Prognosis, 1993)*

Acute symptomatic—Status epilepticus in a previously neurologically normal child, within a week of an underlying etiology including CNS infection, prolonged febrile seizures, encephalopathy, head trauma, cerebrovascular disease, and metabolic or toxic derangements

Remote symptomatic—Status epilepticus in the absence of an identified acute insult but with a history of a pre-existing CNS abnormality more than 1 week before

Idiopathic epilepsy related—Status epilepticus that is not symptomatic and occurred in children with a prior diagnosis of idiopathic epilepsy or when the episode of status epilepticus is the second unprovoked seizure that has led to a diagnosis of idiopathic epilepsy

Cryptogenic epilepsy related—Status epilepticus that is not symptomatic and occurred in children with a prior diagnosis of cryptogenic epilepsy or when the episode of SE is the second unprovoked seizure that has led to a diagnosis of cryptogenic epilepsy

Unclassified—Status epilepticus that cannot be classified into any other group



# Pathophysiology



- Imbalance between excitatory and inhibitory neurotransmitters
- Internalization of GABA receptors with time
- Inefficacy of benzodiazepines after crossing therapeutic window

# Consequences of SE- Depend on it's etiology

- Secondary epilepsy
- Cognitive deterioration
- Behavioral problems
- Focal neurological deficits
- Death (2.7-5.2%)- (higher in PICU cases)
- Most studies relate the outcome of CONVULSIVE status epilepticus

Table 2. Etiology and Mortality Associated With Status Epilepticus in Children and Adults

Etiology	Status Epilepticus Cases	Mortality (events), n
Children		
Infection	52	5
Remote etiologies	38	0
Low levels of antiepileptic drugs <sup>a</sup>	21	0
Cerebrovascular disease	10	0
Metabolic	7	0
Hypoxia	5	0
Idiopathic	5	0
Central nervous system infection	2	0
Drug overdose	2	0
Alcohol related	0	0
Anoxia	0	0
Hemorrhage	0	0
Trauma	0	0
Tumor	0	0
Adults		
Low levels of antiepileptic drugs <sup>a</sup>	34	4
Remote etiologies <sup>b</sup>	25	14
Cerebrovascular disease	22	33
Metabolic	15	30
Alcohol related	13	20
Hypoxia	13	53
Infection	7	10
Tumor	7	30
Anoxia	5	71
Central nervous system infection	3	0
Drug overdose	3	25
Idiopathic	3	25
Trauma	3	25
Hemorrhage	1	0

SOURCE: Adapted with permission from DeLorenzo RJ, Pellock JM, Towne AR, Booss GL.<sup>11</sup>

# Goals of treating SE



- ❖ **Regardless of category:**

  - Abort seizures (on site/ in home treatment)

  - Treat inciting cause

- ❖ Monitor hydration, electrolyte balance, cardiocirculatory and pulmonary functions

- ❖ Administer **rapid IV infusions** of antiepileptic drugs

# Treatment of seizures begins on site

- First aid
- Benzodiazepines: mucosal
  - Rectal diazepam  
(0.3-0.5 mg/kg/dose)
  - Mucosal midazolam  
(0.2-0.3 mg/kg/dose)
- Transfer to ER



# J Sch Nurs. 2007 Jun;23(3):158-65

## **Emergency management of seizures in the school setting.**

- Effective seizure management in the school setting is a critical issue for students with seizures, as well as their parents, classmates, and school personnel. The unpredictable nature of seizures and the potential outcomes of experiencing a seizure in school are sources of anxiety for students with seizures. The ability to respond appropriately to a seizure is of concern to parents and school personnel. Implementation of a seizure emergency treatment plan empowers school personnel to quickly treat the child. Diazepam rectal gel is commonly used in seizure emergency treatment plans. It is safe and effective in terminating seizures and reduces the time to treatment and the need for emergency department visits when used in the school setting, and can be administered by medical and delegated to trained nonmedical personnel. School nurses should be aware of the laws and professional recommendations that pertain to rectal medication administration in schools for optimal emergency seizure management.

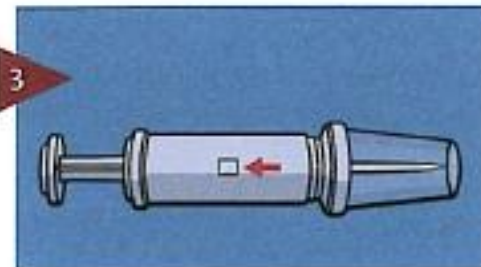
# CHILD ADMINISTRATION INSTRUCTIONS



1 Put person on their side where they can't fall.



2 Get medicine.



3 Get syringe. Note: seal pin is attached to the cap.



4 Push up with thumb and pull to remove cap from syringe. **Be sure seal pin is removed with the cap.**



5 Lubricate rectal tip with lubricating jelly.



6 Turn person on side facing you.



7 Bend upper leg forward to expose rectum.



8 Separate buttocks to expose rectum.



9 Gently insert syringe tip into rectum.  
Note: rim should be snug against rectal opening.

**SLOWLY...**

**COUNT OUT LOUD TO THREE...1...2...3**



# My bias- IN midazolam



- Where is the data ?( pharmacodynamic/ pharmacokinetic)
- Has it been studied in children?
- What is the efficacy?
- What is it's safety?



# We know about it 's use -intranasal for sedation

- 1: **Pediatr Emerg Care. 2008 May;24(5):300-3. Links**
  - Atomized intranasal midazolam use for minor procedures in the pediatric emergency department.
  - [Lane RD](#), [Schunk JE](#).
  - Division of Pediatric Emergency Medicine, Department of Pediatrics, University of Utah, Salt Lake City, UT 84158, USA. [roni.lane@hsc.utah.edu](mailto:roni.lane@hsc.utah.edu)
  - **BACKGROUND:** Procedural sedation is increasingly more common in pediatric emergency departments. We report our experience with intranasal midazolam (INM) using a unique atomization delivery device, specifically the efficacy and safety of this method of sedation. **METHODS:** We performed a retrospective chart review of children who received INM sedation in the emergency department from April 1, 2005, through June 30, 2005. All children aged 1 to 60 months who received INM as the initial means of sedation were eligible for the study. Patients were excluded if they were older than 60 months. **RESULTS:** There were 205 patients who received INM for sedation and who met the study criteria. The mean age was 31.3 +/- 13.2 months (range, 1.5-60 months). The mean and median initial INM dose was 0.4 mg/kg (range, 0.3-0.8 mg/kg). Laceration repair was the most common procedure necessitating sedation (89%). The median degree-of-sedation score achieved was 2.0 (anxiolysis). Eleven patients (5.4%; 95% CI, 3%-9%) required an additional sedative to complete the procedure. Ten of the 11 patients received ketamine as the adjunctive sedative, and 1 patient required additional INM. The average time of last oral intake to start of sedation was 3.5 hours (range, 0.5-10.0 hours). Thirty six patients (18%) were NPO for 2 hours or less. There was 1 adverse event (0.5%; 95% CI, 0%-3%). This was a minor desaturation episode following ketamine administration requiring brief blow by oxygen. There were no adverse events (0%; 95% CI, 0%-2%) in patients who received INM alone. **CONCLUSION:** We conclude that atomized INM is effective in providing anxiolysis to children undergoing minor procedures in the pediatric emergency department. We are encouraged that no adverse events occurred with the use of INM alone despite relatively short fasting times.



# Pharmacokinetic data re: IN midazolam

Vol. 6, 352-358, April 2009 © The American Society for Experimental NeuroTherapeutics, Inc.

*Neurotherapeutics: The Journal of the American Society for Experimental NeuroTherapeutics*

## Intranasal Delivery of Antiepileptic Medications for Treatment of Seizures

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Intranasal administration of antiepileptic medications, in particular benzodiazepines, has been studied with various preparations. Intranasal midazolam has been extensively studied in epilepsy patients and is recommended in some consensus guidelines as an alternative drug delivery technique for prompt treatment.<sup>10-12</sup>

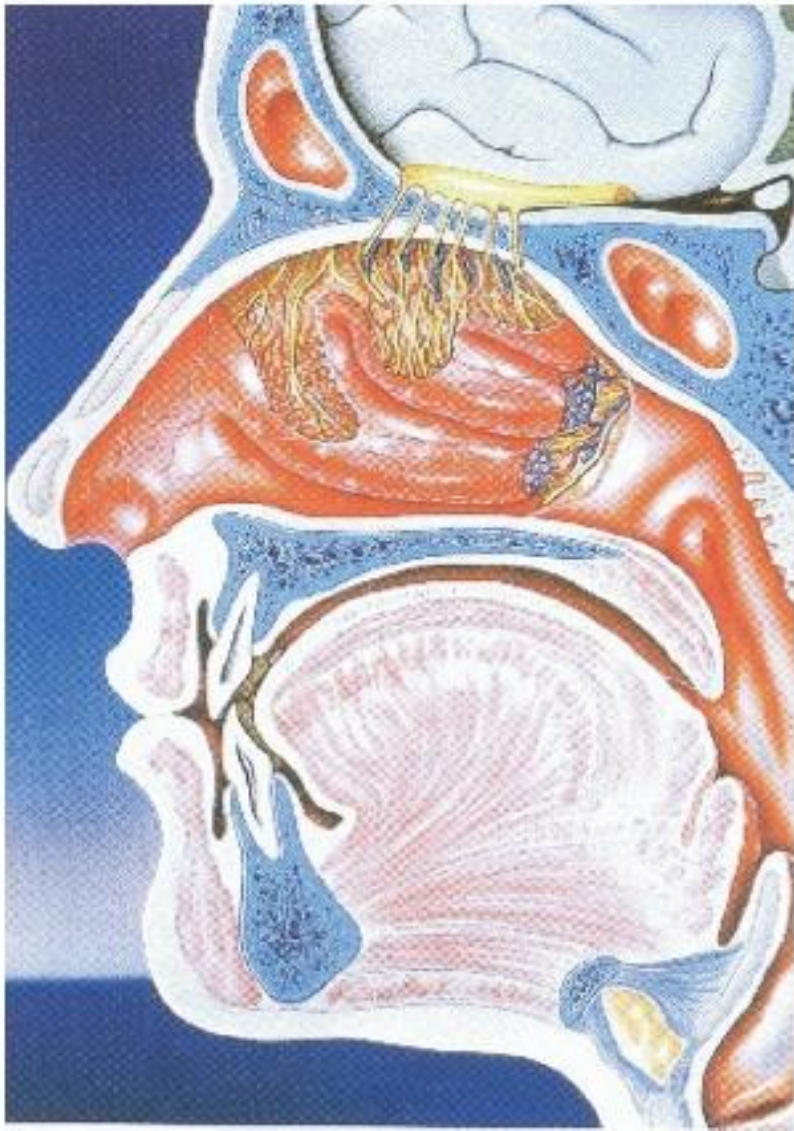


FIG. 1. Anatomy of the nasal cavity and relation to the brain.

**Table 1. Chemistry and Formulation Issues Affecting Intranasal Medication Bioavailability and Tolerability**

- Potent medication, <20 mg per dose
- Molecular weight, <1000 Daltons
- Excellent water solubility
- pKa and pH control of aqueous solutions
- Osmolality—isotonic to slightly hypertonic
- Stability in processing and storage
- Compatibility with sprayer components
- Use of special excipients to manage
  - Solubility
  - Stability
  - Permeation



Intracellular/ paracellular  
 Olfactory nerve  
 180cm sq area  
 Drop/spray  
 Physical obstruction/  
 mucus

# Is this something new?

Items 1 - 20 of 61

of 4 [Next](#)

1:

[Intranasal midazolam therapy for pediatric status epilepticus.](#)

Wolfe TR, Macfarlane TC.

[Am J Emerg Med](#). 2006 May;24(3):343-6. Review.

PMID: 16635708 [PubMed - indexed for MEDLINE]

[Related Articles](#)

2:

[Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: a randomised trial.](#)

Scott RC, Besag FM, Neville BG.

[Lancet](#). 1999 Feb 20;353(9153):623-6.

PMID: 10030327 [PubMed - indexed for MEDLINE]

[Related Articles](#)

3:

[Comparison of intranasal midazolam with intravenous diazepam for treating acute seizures in children.](#)

Mahmoudian T, Zadeh MM.

[Epilepsy Behav](#). 2004 Apr;5(2):253-5.

PMID: 15123028 [PubMed - indexed for MEDLINE]

[Related Articles](#)

4:

[Community use of intranasal midazolam for managing prolonged seizures.](#)

Kyrkou M, Harbord M, Kyrkou N, Kay D, Coulthard K.

[J Intellect Dev Disabil](#). 2006 Sep;31(3):131-8.

PMID: 16954090 [PubMed - indexed for MEDLINE]

• [Related Articles](#)

5:

[Buccal route for benzodiazepines in treatment of seizures?](#)

Holmes GL.

[Lancet](#). 1999 Feb 20;353(9153):608-9. No abstract available.

PMID: 10030323 [PubMed - indexed for MEDLINE]

[Related Articles](#)

6:

[Nasal benzodiazepines for management of acute childhood seizures?](#)

Wallace SJ.

[Lancet](#). 1997 Jan 25;349(9047):222. No abstract available.

PMID: 9014904 [PubMed - indexed for MEDLINE]

[Related Articles](#)

7:

[Use of intranasal midazolam to treat acute seizures in paediatric community settings.](#)

PMID: 17013785 [PubMed - indexed for MEDLINE]

Harbord MG, Kyrkou NE, Kyrkou MR, Kay D, Coulthard KP.

[J Paediatr Child Health](#). 2004 Sep-Oct;40(9-10):556-8.

PMID: 15367152 [PubMed - indexed for MEDLINE]

[Related Articles](#)

8:

# Where are the articles from?

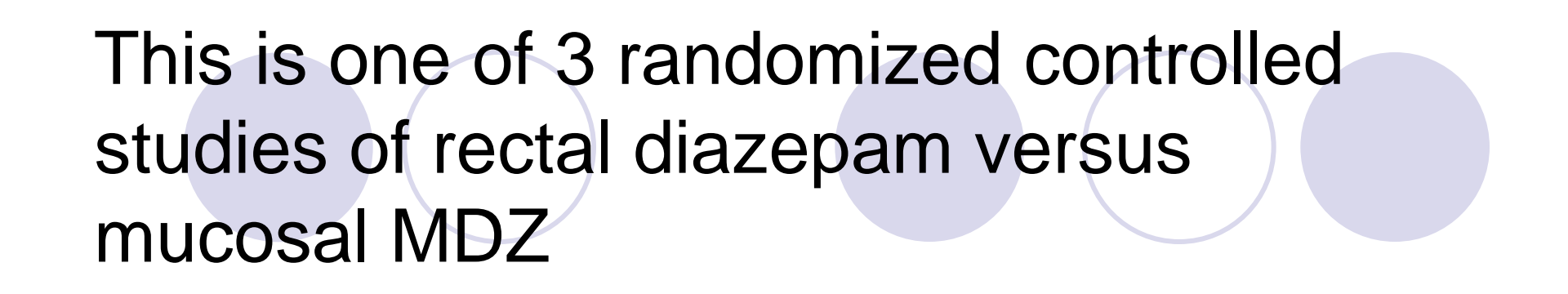
- UK
- Israel
- Turkey
- Australia
- Africa
- India
- Japan
- USA

**Effects of intranasal midazolam and rectal diazepam on acute convulsions in children: prospective randomized study.**

[Fişgin T](#), [Gurer Y](#), [Teziç T](#), [Senbil N](#), [Zorlu P](#), [Okuyaz C](#), [Akgün D](#).

Pediatric Neurology Department, Dr Sami Ulus Child Health and Disease Centre, Telsizler-Ankara, Turkey. [figint@turk.net](mailto:figint@turk.net)

- In this study, the effects and side effects of rectal diazepam and intranasal midazolam were compared in the treatment of acute convulsions in children to develop a practical and safe treatment protocol. In the diazepam group, the seizures of 13 (60%) patients terminated in 10 minutes; however, 9 (40%) patients did not respond. In the midazolam group, 20 (87%) patients responded in 10 minutes, but 3 (13%) patients did not respond. Regarding the anticonvulsant effect, midazolam was found to be more effective than diazepam, and the difference was statistically significant ( $P < .05$ ). The necessity of a second drug for the seizures that did not stop with the first drug was higher in the diazepam group than the midazolam group, and the difference was statistically significant ( $P < .05$ ). We conclude that as an antiepileptic agent, intranasal midazolam is more effective than rectal diazepam. After administration, we did not observe any serious complications. Further investigations are necessary; however, intranasal administration is easy, so if the nasal drop and spray forms used in some European countries and the United States are available worldwide, it will be very useful for physicians in the emergency room



This is one of 3 randomized controlled studies of rectal diazepam versus mucosal MDZ

- Aborted 87% seizures
- No side effects
- What about the fact that IV benzos are actually considered first line therapy??

# IV benzos versus IN MDZ



- 2 randomized studies
- Lahat et al- compared IV diazepam to IN Midazolam
- MDZ stopped seizures in 6 minutes in 88% patients and IV diazepam in 8 minutes in 92% patients
- No difference in noted side effects in 2 arms



**Comparison of intranasal midazolam with intravenous diazepam for treating acute seizures in children.**

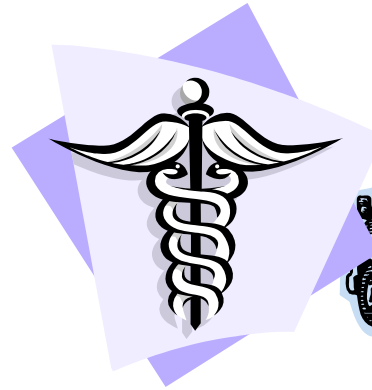
[Mahmoudian T](#), [Zadeh MM](#).

Department of Child Neurology, Medical University of Isfahan, Isfahan, Iran.

[t\\_mahmoudian@med.mui.ac.ir](mailto:t_mahmoudian@med.mui.ac.ir)

- Midazolam, a water-soluble benzodiazepine, is usually given intravenously in status epilepticus. The aim of this study was to determine whether intranasal midazolam is as safe and effective as intravenous diazepam in the treatment of acute childhood seizures. Seventy children aged 2 months to 15 years with acute seizures (febrile or afebrile) admitted to the pediatric emergency department of a general hospital during a 14-month period were eligible for inclusion. Intranasal midazolam 0.2 mg/kg and intravenous diazepam 0.2 mg/kg were administered after intravenous lines were established. Intranasal midazolam and intravenous diazepam were equally effective. The mean time to control of seizures was 3.58 (SD 1.68) minutes in the midazolam group and 2.94 (SD 2.62) in the diazepam group, not counting the time required to insert the intravenous line. No significant side effects were observed in either group. Although intranasal midazolam was as safe and effective as diazepam, seizures were controlled more quickly with intravenous diazepam than with intranasal midazolam. Intranasal midazolam can possibly be used not only in medical centers, but also in general practice and at home after appropriate instructions are given to families of children with recurrent seizures.

Vitals??



## Intranasal midazolam vs rectal diazepam in acute childhood seizures.

[Bhattacharyya M](#), [Kalra V](#), [Gulati S](#).

Department of Pediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India. madhumita57@yahoo.co.in

- One hundred eighty-eight seizure episodes in 46 children were randomly assigned to receive treatment with rectal diazepam and intranasal midazolam with doses of 0.3 mg/kg body weight and 0.2 mg/kg body weight, respectively. Efficacy of the drugs was assessed by drug administration time and seizure cessation time. Heart rate, blood pressure, respiratory rate, and oxygen saturation were measured before and after 5, 10, and 30 minutes following administration of the drugs in both groups. Mean time from arrival of doctor to drug administration was 68.3 +/- 55.12 seconds in the diazepam group and 50.6 +/- 14.1 seconds in the midazolam group (P = 0.002). Mean time from drug administration to cessation of seizure was significantly less in the midazolam group than the diazepam group (P = 0.005). Mean heart rate and blood pressure did not vary significantly between the two drug groups. However, mean respiratory rate and oxygen saturation differed significantly between the two drug groups at 5, 10, and 30 minutes after drug administration. Intranasal midazolam is preferable to rectal diazepam in the treatment of acute seizures in children. Its administration is easy, it has rapid onset of action, has no significant effect on respiration and oxygen saturation, and is socially acceptable.

# Changes in vitals after diazepam versus midazolam

- Changes in heart rate, respiratory rate, blood pressure, and oxygen saturation, as measured at 5-minute, 10-minute, and 30-minute intervals after administration of drugs in both groups, revealed that mean heart rate and blood pressure changes were not statistically different. Mean respiratory rate decreased by 1/minute at 5 minutes and 4/minute at 10 and 30 minutes after administration of rectal diazepam from predrug mean respiratory rate, whereas there was no decrease of mean respiratory rate at 5/minutes and a decline of only 1/minute at 10 minutes and 30 minutes after administration of intranasal midazolam. By repeated-measures of analysis of variance, it was found that changes in respiratory rate differed significantly between the rectal diazepam group and the intranasal midazolam group at 10 minutes and 30 minutes after drug administration, with  $P = 0.027$  and  $P = 0.039$ , respectively.

## Buccal midazolam

This information should be read in conjunction with any patient information leaflet provided by the manufacturer.

**This fact sheet explains about buccal midazolam, how it is given and some of its possible side effects.**

### What is midazolam?

Midazolam belongs to a group of medicines called benzodiazepines, which are used to treat a number of different conditions. One of these is status epilepticus. Status epilepticus is a condition where a person has a seizure (convulsion or fit) or a series of seizures that last for 30 minutes or more, without a complete recovery of consciousness. If a seizure lasts for more than five minutes, it may be difficult to stop unless treatment is given. It is therefore important that rapid treatment is given to stop the seizures and therefore prevent status epilepticus.

Midazolam is chemically related to diazepam, which is another medicine used to treat seizures. In emergencies, diazepam is often given by the rectal route. This can be useful in many situations, but at times, it may not be convenient. In situations where it is not acceptable or convenient to use rectal diazepam, buccal midazolam becomes necessary.

### How is it given?

Midazolam is available in various forms as follows:

- The buccal route is where the medicine is placed against the sides of the gums and cheek. The medicine is absorbed directly into the bloodstream. The medicine does not need to be swallowed, but if swallowed accidentally will cause no harm.
- Midazolam is also available as an injection (10mg in 2ml) in a glass ampoule. This product is used to give midazolam by the buccal route.
- It is also available in a preparation called Epistatus®, a sugar-free buccal liquid. The strength is 10mg in 1ml. There are four 10mg doses in each bottle and four syringes are provided with it.

**Unexpected complications of intranasal midazolam premedication.**

[Uzun S](#), [Dal D](#).

PMID: 17596238 [PubMed - indexed for MEDLINE]

- We present three children aged 4, 5 and 6 years old, scheduled for eye examination under general anesthesia and who developed unexpected reactions to intranasal midazolam premedication. The normal i.v. solution of midazolam ( $0.7 \text{ mg} \cdot \text{kg}^{-1}$ ) was administered via a 5-ml syringe to the nostrils. Two developed facial flushing and itchy urticarial patches on the face around the eyes, neck and body, 10 min after the drug administration, before any other drug had been given. The 6-year-old child developed severe itching, burning and pain sensation around the anal region without any flushing or urticarial patches on the body 5 min after the intranasal midazolam and before any other drug had been given. They had no other systemic symptoms and no history of allergy to midazolam or any other medicaments. They subsequently received general anesthesia with sevoflurane induction in O<sub>2</sub> and N<sub>2</sub>O. The symptoms were treated with i.v. diphenylhydramine (10 mg) and i.v. prednisolone (25 mg) and the urticarial patches resolved. For anal burning sensation and pruritus, cold swabbings were applied to this region. All the children were discharged without other complications.

# Prehospital Intranasal Midazolam for the Treatment of Pediatric Seizures

*Maija Holsti, MD, MPH,\* Benjamin L. Sill, BS,† Sean D. Firth, PhD, MPH,‡ Francis M. Filloux, MD,§ Steven M. Joyce, MD,|| and Ronald A. Furnival, MD\**

*Pediatric Emergency Care* • Volume 23, Number 3, March 2007



**TABLE 1.** Comparison of Midazolam and Diazepam Protocols

Instructions	Midazolam	Diazepam
Preparation	Apply oxygen Suction nose if there are secretions	Apply oxygen
Indication	Seizure >5 min	Seizure >5 min
Dose	0.2 mg/kg	0.3–0.5 mg/kg
Route	Intranasal: divided into each nares using the MAD	Rectal
Maximum dose	10 mg	20 mg
Repeat dose	0.2 mg/kg 5 min after first dose	0.25 mg/kg if seizure persists



**TABLE 2.** Demographic Data and Seizure Time for Patients Treated With IN-MAD Midazolam and PR Diazepam

Characteristics	IN Midazolam	PR Diazepam	<i>P</i>
Demographic data			
No. patients (n = 57)	39	18	—
Median age	4.5 yrs	2.9 yrs	0.27*
Age range	8 mo–16 yrs	1–17 yrs	
Male, n (%)	18 (46)	10 (56)	0.51†
History of seizures, n (%)	<u>32 (82)</u>	<u>12 (67)</u>	0.20†
History of anticonvulsants, n (%)	<u>24 (62)</u>	<u>12 (67)</u>	0.71†
Median dose of medication given (mg/kg)	<u>0.2</u>	<u>0.3</u>	—
Range of dose given (mg/kg)	0.1–0.4	0.1–0.7	—
EMS-witnessed seizure time (min)			
Median (n)	<u>11 (25)</u>	30 (13)	0.003*
Range	1–50	5–80	—
Total seizure time (min)			
Median (n)	<u>25 (36)</u>	<u>45 (17)</u>	<0.001*
Range	4–105	25–480	—
Median total hospital charges (\$)	<u>1459</u>	<u>6980</u>	<0.0001*

\*Mann-Whitney *U* test.

† $\chi^2$  test.



# Off label use

## DEFINITION: OFF-LABEL USE

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Use for indication, dosage form, dose regimen, population or other use parameter not mentioned in the approved labeling.

# FDA off label use for an FD approved drug

## FDA POLICIES ON OFF-LABEL USE (con't)

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- ◆ FDA recognizes that off-label use of drugs by prescribers is often appropriate and may represent the standard of practice.
- ◆ Prescribers and other parties may obtain, upon request, information on off-label uses from pharmaceutical firms. (Policy on solicited information)



# FDA information sheet on off label use

U.S. Food and Drug Administration

## INFORMATION SHEETS

**Guidance for Institutional Review Boards and Clinical Investigators  
1998 Update**

### **"Off-Label" and Investigational Use Of Marketed Drugs, Biologics, and Medical Devices**

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#### **"Off-Label" Use of Marketed Drugs, Biologics and Medical Devices**

Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgement. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects. Use of a marketed product in this manner when the intent is the "practice of medicine" does not require the submission of an Investigational New Drug Application (IND), Investigational Device Exemption (IDE) or review by an Institutional Review Board (IRB). However, the institution at which the product will be used may, under its own authority, require IRB review or other institutional oversight.



# Questions already submitted

- We have talked to our medical director regarding the treatment Dr. Joshi has prescribed. Our medical director agrees that we are not equipped in the school setting for the adverse effects that the treatment may cause. We do not have oxygen or "crash cart" medicines or equipment. Should Dr. Joshi be talking to the MDs as well?
- A school is not equipped with oxygen and cardiac monitoring devices to use in case of an emergency resulting from medication administration
- Is intranasal midazolam an off label use of the medication?
- Iowa Emergency response providers have declined to administer and do not have a protocol. What can we do?
- Reports of administration: One school plan is for the father (an MD) to come to the school if medication is needed
- How can the school provide the needed several hour post administration observation and also consider the needs of the rest of the students

